X11594 BC

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/14, A61K 31/40 — A1

(11) International Publication Number: **WO 97/08167**

(43) International Publication Date: 6 March 1997 (06.03.97)

(21) International Application Number: PCT/EP96/03512

(22) International Filing Date: 6 August 1996 (06.08.96)

(30) Priority Data:
9517559.2 26 August 1995 (26.08.95) GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventor; and

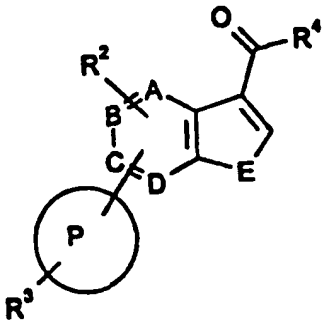
(75) Inventor/Applicant *(for US only)*: FORBES, Ian, Thomson [GB/GB]; New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: SUMMERSELL, Richard, John; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BP (GB).

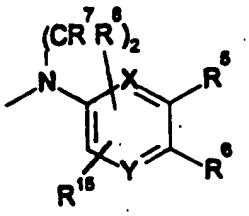
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

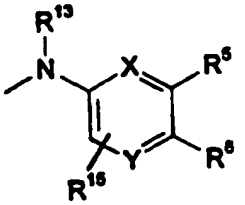
(54) Title: $5HT_{2C}$ AND $5HT_{2B}$ ANTAGONISTS



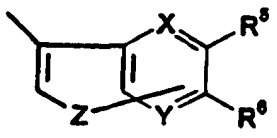
(I)



(i)



(ii)



(iii)

(57) Abstract

Compounds of formula (I) or a salt thereof, wherein R^4 is a group of formula (i), a group of formula (ii) or a group of formula (iii) have been found to have $5HT_{2C}$ receptor antagonist activity. Some or all of the compounds of the invention also exhibit $5HT_{2B}$ antagonist activity. $5HT_{2C/2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

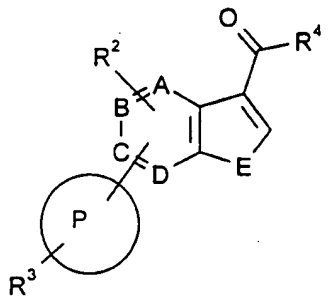
AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

5HT2C AND 5HT2B ANTAGONISTS

This invention relates to compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

WO 94/04533 (SmithKline Beecham plc) describes indole and indoline derivatives which are described as possessing $5HT_{2C}$ receptor antagonist activity. A structurally distinct class of compounds has now been discovered, which have been found to have $5HT_{2C}$ receptor antagonist activity. Some or all of the compounds of the invention also exhibit $5HT_{2B}$ antagonist activity. $5HT_{2C/2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

wherein:

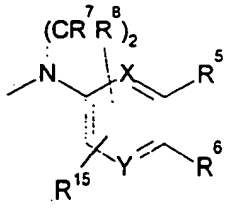
A,B,C and D are all carbon, or one of A,B,C or D is nitrogen and the others are carbon;

E is oxygen, sulphur, CH_2 or NR^1 where R^1 is hydrogen or C_{1-6} alkyl;

P is a phenyl or an optionally substituted 5-7-membered heterocyclic ring containing one to three heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylthio, CF_3, NR^9R^{10} or OR^{11} where R^9, R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or arylC_{1-6} alkyl; and

R^4 is a group of formula (i)



(i)

in which:

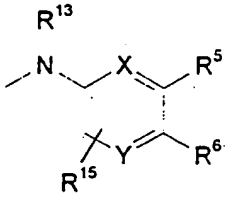
X and Y are both nitrogen, one is nitrogen and the other is carbon or a CR^{14} group or one is a CR^{14} group and the other is carbon or a CR^{14} group;

R^5, R^6, R^{14} and R^{15} groups are independently hydrogen, C_{1-6} alkyl optionally substituted by one or more halogen atoms, C_{2-6} alkenyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyloxy, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-6} alkylthio, C_{3-6} cycloalkylthio, C_{3-6} cycloalkyl-C_{1-6} alkylthio, C_{1-6}alkoxy, hydroxy, halogen, nitro, CF_3, C_2F_5, OCF_3, SCF_3, SO_2CF_3, SO_2F, formyl, C_{2-6} alkanoyl, cyano, optionally substituted phenyl or thienyl, NR^9R^{10}or $CONR^9R^{10}$ where R^9 and R^{10} are as defined for R^1, CO_2R^{12} where R^{12} is hydrogen or C_{1-6} alkyl;

or R^5 and R^6 form part of an optionally substituted 5-membered carbocyclic or heterocyclic ring;

R^7 and R^8 are independently hydrogen or C_{1-6} alkyl; or

R^4 is a group of formula (ii):

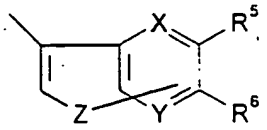


(ii)

in which X and Y are both nitrogen, one is nitrogen and the other is a CR^{14} group or X and Y are both CR^{14} groups and R^5, R^6, R^{14} and R^{15} are as defined in formula (i); and

R^{13} is hydrogen or C_{1-6} alkyl, or

R^4 is a group of formula (iii):



in which R^5, R^6, X and Y are as defined for formula (i) and Z is oxygen, sulphur, CH_2 or NR^{13} where R^{13} is hydrogen or C_{1-6} alkyl.

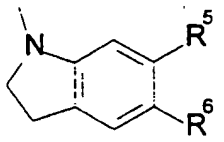
C_{1-6} Alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Preferably P is pyridyl, in particular a 3-pyridyl or 4-pyridyl group.

Preferably E is NR^1 where R^1 is hydrogen.

Preferably R^2 is hydrogen.

Preferably R^4 is a group of formula (i). Preferably X and Y form part of a phenyl ring, that is to say one of X or Y is carbon and the other is a CH group or both of X and Y are CH groups. Most preferably R^4 is an indoline ring, that is to say a group of formula (A):



(A)

in which R^5 and R^6 are as defined in formula (i).

When R^5 and R^6 form part of an aromatic ring suitable rings include thiophene, furan and pyrrole rings. Preferred R^5 and R^6 groups, which can be the same or different, include C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, CF_3, and CO_2R^{11} where R^{11} is hydrogen or C_{1-6} alkyl Preferably R^5 is trifluoromethyl or chloro and R^6 is C_{1-6}alkylthio, C_{1-6}alkyl or C_{1-6}alkoxy.

Particularly preferred compounds of the invention include:
1-(5-(3-Pyridyl)-3-indolylcarbonyl-5-methoxy-6-trifluoromethylindoline,
1-(5-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
1-(6-(3-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
1-(6-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
and pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic. Quaternary salts of intermediate compounds in which P is an

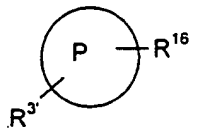
aromatic group such as pyridyl can also be prepared with C_{1-6}alkylating agents, for example methyl iodide, and such salts also form an aspect of the invention.

Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

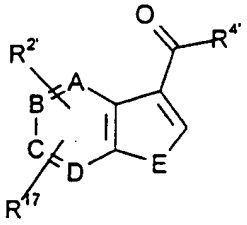
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



(II)

with a compound of formula (III);

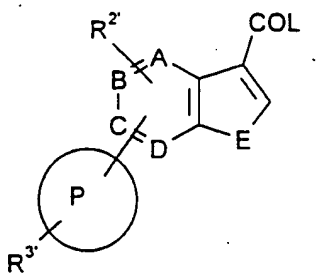


(III)

wherein R^{16} and R^{17} contain the appropriate functional group(s) necessary to form a bond when coupled, A, B, C, D and P are as defined in formula (I), E is as defined in formula (I) or is a group $NR^{1'}$ and the variables, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^1, R^2, R^3 and R^4 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3

and R^4, interconverting R^1, R^2, R^3 and R^4 and forming a pharmaceutically acceptable salt thereof, or

(b) coupling a compound of formula (IV):



(IV)

wherein P, A, B, C, D, E, $R^{2'}$ and $R^{3'}$ are as defined above and L is a leaving group with a compound of formula (V):

$$R^{4'}\text{-}H \qquad (V)$$

wherein $R^{4'}$ is as defined above and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3 and R^4, interconverting R^1, R^2, R^3 and R^4 and forming a pharmaceutically acceptable salt thereof.

Preferably R^{17} is a leaving group such as halogen and in particular bromo.

Preferably R^{16} is a boronic acid group. Compounds of formula (II) and (III) are reacted together using standard boronic acid coupling conditions in the presence of an organometallic catalyst. Preferred catalysts are palladium catalysts, in particular tetrakis (triphenylphosphine) palladium(0).

For process (b) L is a leaving group such as halogen, in particular chloro. Compounds of formula (IV) and (V) can be reacted together using standard reaction conditions known in the art.

R^1 to R^3 groups can be introduced at any suitable stage in the process, preferably R^1 to R^3 groups are introduced at an early stage in the process. It should be appreciated that it is preferred that all groups R^1 to R^3 are introduced before coupling compounds of formula (II) and (III).

Suitable examples of groups $R^{1'}$, $R^{2'}$ and $R^{3'}$ which are convertible to R^1, R^2 and R^3 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed

by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation.

Interconversions of R^1, R^2 and R^3 are carried out by conventional procedures. For example halo groups can be introduced by selective halogenation of the ring P or the benzene ring of the indoline group using conventional conditions. It should be appreciated that it may be necessary to protect any R^1 to R^3 hydrogen variables which are not required to be interconverted.

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formula (II), (III), (IV) and (V) may be prepared according to known methods or analogous to known methods.

Novel intermediates of formula (III) and (IV) also form part of the invention.

Parmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2B/2C}$ receptor antagonist activity and are believed to be of potential use for the treatment or prophylasis of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight

of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 70.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

1-Methoxy-4-nitro-2-trifluoromethylbenzene (D1)

Sodium (11.78g, 0.512 mol) was dissolved in dry methanol (1 l) and to the resulting solution was added a solution of 1-chloro-4-nitro-2-trifluoromethyl-benzene (96.22g, 0.427 mol) in methanol (100 ml). The reaction mixture was refluxed for 3 h then cooled and evaporated *in vacuo*. The residue was partitioned between water (500 ml) and dichloromethane (3 x 400 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to give the title compound (93.76g, 99%) as a white solid.

NMR ($CDCl_3$) δ: 4.05 (3H, s), 7.12 (1H, d), 8.45 (1H, dd), 8.52 (1H, d).

Description 2

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D2)

A mixture of 1-methoxy-4-nitro 2-trifluoromethylbenzene (D1) (93g, 0.421 mol) and 4-chlorophenoxyacetonitrile (77.55g, 0.463 mol) in dry DMF (500 ml) was added dropwise over 0.75 h to a stirred solution of KO^tBu (103.85g, 0.927 mol) in dry DMF (400 ml) at -10° C. After complete addition the resulting purple solution was maintained at -10° C for 1 h then poured into a mixture of ice/water (1.5 l) and 5 M aqueous HCl (1.5 l). The resulting mixture was extracted with dichloromethane (3 x 1 l). The combined extracts were washed with water (3 l), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica using 10-40% ethyl acetate/petroleum ether as eluant to give the crude product which was recrystallised from ethyl acetate/petroleum ether to afford the title compound (85.13g, 78%) as a white solid. Mp 103-104 °C.

NMR ($CDCl_3$) δ: 4.10 (3H, s), 4.37 (2H, s), 7.34 (1H, s), 8.53 (1H, s).

Description 3

5-Methoxy-6-trifluoromethylindole (D3)

(5-Methoxy-2-nitro-4-trifluoromethylphenyl)acetonitrile (D2) (85g, 0.327 mol) in ethanol/water (9:1, 1.6 l) and glacial acetic acid (16 ml) was hydrogenated over 10% palladium on carbon (50 g) at 50 psi for 0.5 h at room temperature. The reaction mixture was filtered and evaporated *in vacuo*. The residue was partitioned between

aqueous K_2CO_3 (1 l) and dichloromethane (2 x 1 l) and the combined organic extract was dried (Na_2SO_4) and evaporated to afford the title indole (67.63g, 96%) as a grey solid.

NMR ($CDCl_3$) δ: 3.94 (3H, s), 6.53 (1H, m), 7.21 (1H, s), 7.32 (1H, m), 7.64 (1H, s), 8.25 (1H, br s).

Description 4

5-Methoxy-6-trifluoromethylindoline (D4)

The indole (D3) (67.63g, 0.315 mol) was treated with sodium cyanoborohydride (40 g, 0.637 mol) in glacial acetic acid (500 ml) using standard procedures to afford the title indoline (67.73g, 99%) as an off-white solid.

NMR ($CDCl_3$) δ: 3.07 (2H, t), 3.58 (2H, t), 3.67 (1H, br s), 3.83 (3H, s), 6.83 (1H, s), 6.88 (1H, s).

Description 5

1-(5-Bromo-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline (D5)

A solution of 5-bromoindole-3-carboxylic acid (A.S. Katner, *Org. Prep. Proced.*, 1970, **2**, 297) (1.13g, 4.7 mmol) in dry tetrahydrofuran (50 mL) was treated with oxalyl chloride (0.43 mL, 5 mmol) and dimethylformamide (5 drops). The mixture was stirred at room temperature for 1 h, then evaporated to dryness. Tetrahydrofuran (25 mL) was added to the residue, followed by 5-methoxy-6-trifluoromethyl indoline (D4, 1.1g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in tetrahydrofuran (25 mL). The mixture was stirred overnight, then poured into water. The precipitate was filtered off, washed with water and dried. The crude product was chromatographed on silica gel eluted with 3-4% methanol/dichloromethane. Eluted product was triturated with dichloromethane/methanol to give the title compound (0.89g, 43%), Mp. >250°C.

NMR (d_6DMSO) δ: 3.28 (2H, t, J=8), 3.88 (3H, s), 4.97 (2H, t, J=8), 7.26 (1H, s), 7.33 (1H, d, J=8), 7.47 (1H, d, J=8), 8.11 (1H, s), 8.29 (1H, s), 8.41 (1H, s)

MS (API): m/z=439 (MH^+, ^{79}Br), 441 (MH^+, ^{81}Br)

$C_{19}H_{14}N_2O_2BrF_3$ requires M+1 = 439 and 441

Description 6

6-Bromo-3-(trichloroacetyl)indole (D6)

A mixture of 6-bromoindole (1.18g, 6.0 mmol), trichloroacetyl chloride (1.0 mL, 9 mmol) and pyridine (0.72 mL, 9 mmol) in dry 1,4-dioxan (12 ml) was stirred overnight at room temperature, then heated at 90°C until the reaction appeared complete by T.L.C. The mixture was poured into water and the precipitate was filtered off, washed with water and dried. The crude product was recrystallised from ethanol/water to give the title compound (1.36g, 66%), Mp. 234-40°C.

NMR (d_6DMSO) δ: 7.47 (1H, dd, J=7,1), 7.80 (1H, d, J=1), 8.23 (1H, d, J=7), 8.64 (1H,s), 12.63 (1H, s).

MS (API) m/z=338, 340, 342, 344 ([M-H]$^-$)

Description 7

6-Bromo-3-indolecarboxylic acid (D7)

A solution of trichloroacetylindole (D6, 1.33g, 3.9 mmol) in methanol containing one drop of 60% aqueous potassium hydroxide was heated under reflux for 3h. Dilute (10%) aqueous sodium hydroxide (10 mL) was added and the mixture was heated under reflux for 2.5 h. Most of the solvent was then removed *in vacuo* and the residue was diluted with water and extracted with dichloromethane. The aqueous phase was then acidified with dilute hydrochloride acid and extracted with dichloromethane/methanol. This extract was dried and evaporated to give the title compound (0.79g, 84%).

NMR (d_6DMSO) δ: 7.32 (1H, dd, J=7,2), 7.68 (1H, s), 7.95 (1H, d, J=7), 8.04 (1H, d, J=2), 11.93 (1H, s), 12.15 (1H, s).

MS (API): m/z=238 ([M-H]$^-$, ^{79}Br), 240 ([M-H]$^-$, ^{81}Br)
$C_9H_6NO_2Br$ requires M-1 = 238 and 240

Description 8

1-(6-Bromo-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline (D8)

The title compound was prepared by the method of Description 5, using 6-bromoindolecarboxylic acid (D7, 0.79g, 3.3 mmol). Chromatography on silica gel

eluted with 3-5% methanol/dichloromethane, followed by trituration with dichloromethane/methanol gave the title compound (0.89g, 61%), Mp. >250° C.

MHR (d_6DMSO) δ: 3.27 (2H, t, J=8), 3.88 (3H, s), 4.95 (2H, t, J=8), 7.28 (2H, m), 7.67 (1H, s), 8.05 (1H, d, J=8), 8.08 (1H, s), 8.49 (1H, s), 11.95 (1H, broad).

MS (API): m/z = 439 (MH^+, ^{78}Br), 441 (MH^+, ^{81}Br)
$C_{19}H_{14}N_2OBrF_3$ requires M+1 = 439 and 441

Example 1

1-(5-(3-Pyridyl)-3-indolylcarbonyl-5-methoxy-6-trifluoromethylindoline (E1)

A mixture of the 5-bromoindolecarboxamide (D5, 0.30g,0.68 mmol), 3-pyridylboronic acid (Chem Pharm Bull 1983, 31(12) 4573) (86 mg, 0.7 mmol), tetrakis (triphenylphosphine) palladium (23 mg, 0.02 mmol) and sodium carbonate (0.28g, 2.7 mmol) in 1,2-dimethoxyethane (20 ml) and water (2 ml) was heated under reflux overnight. The mixture was then cooled and poured into water. The precipitate was filtered off, washed with water and dried. The residue was chromatographed on silica gel eluted with 4-5% methanol/ dichloromethane to give the title compound (0.21g, 71%), Mp. >250°C.

NMR (d_6DMSO) δ : 3.28 (2H, t, J=8), 3.88 (3H, s), 4.48 (2H, t, J=8), 7.27 (1H, s), 7.48 (1H, dd, J=7, 5), 7.56 (1H, d, J=8), 7.62 (1H, d, J=8), 8.08 (1H, d, J=7), 8.11 (1H, d, J=2), 8.39 (1H, s), 8.42 (1H, s), 8.54 (1H, d, J=5), 8.89 (1H, s).

MS (API): Found m/z 438 (MH^+)
$C_{24}H_{18}N_3O_2F_3$ requires M+1 = 438

Example 2

1-(5-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline (E2)

The title compound was prepared by the method of Example 1, using 4-pyridylboronic acid (Rec Trav Chim Pay Bas 1965, 84, 439) (0.10g, 0.81 mmol). Chromatography and recrystallisation from methanol gave the title compound (0.08g, 27%), Mp. >250°C.

NMR (d_6DMSO) δ: 3.28 (2H, t, J=8), 3.89 (3H, s), 4.49 (2H, t, J=8), 7.28 (1H, s), 7.62 (1H, d, J=8), 7.67 (1H, d, J=8), 7.72 (2H, d, J=7), 8.13 (1H, s), 8.42 (1H, s), 8.52 (1H, s), 8.61 (2H, d, J=7), 12.03 (1H, s).

MS (API): Found m/z 438 (MH^+)
$C_{24}H_{18}N_8O_2F_3$ requires M+1 = 438

Example 3

1-(6-(3-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline (E3)

The title compound was prepared by the method of Example 1, using the 6-bromoindolecarboxamide (D8, 0.30g, 0.68 mmol) and 3-pyridylboronic acid (92 mg, 0.75 mmol). Recrystallisation from dichloromethane/methanol gave the title compound (0.15g, 50%), Mp. 242°C (decomp.)

NMR (d_6DMSO) δ: 3.28 (2H, t, J=8), 3.88 (3H, s), 4.49 (2H, t, J=8), 7.28 (1H, s), 7.50 (2H, m), 7.79 (1H, s), 8.10 and 8.13 (2H, s+d), 8.21 (1H, d, J=8), 8.42 (1H, s), 8.57 (1H, d, J=5), 8.94 (1H, s), 12.00 (1H, s).

MS (API): Found m/z 438 (MH^+)
$C_{24}H_{18}N_3O_2F_3$ requires M+1 = 438

Example 4

1-(6-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline (E4)

The title compound was prepared by the method of Example 1, using the 6-bromoindolecarboxamide (D8, 0.40g, 0.9 mmol) and 4-pyridylboronic acid (0.27g, 2.2 mmol). Chromatography on silica gel, eluted with 3-6% methanol/dichloromethane gave the title compound (0.17g, 43%), Mp. >250°C.

NMR (d_6DMSO/d_6-acetone) δ: 3.29 (2H, t, J=8), 3.88 (3H, s), 4.50 (2H, t, J=8), 7.25 (1H, s), 7.61 (1H, d, J=8), 7.75 (2H, d, J=7), 7.88 (1H, s), 8.14 (1H, d, J=2), 8.25 (1H, d, J=8), 8.44 (1H, s), 8.62 (2H, d, J=7), 12.05 (1H, s).

MS (API): m/z=438
$C_{24}H_{18}N_3O_2F_3$ requires M+1 = 438

Found: C, 65.14; H, 4.33; N, 9.49%

$C_{24}H_{18}N_3O_2F_3$ requires C, 65.90; H, 4.15; N, 9.61%

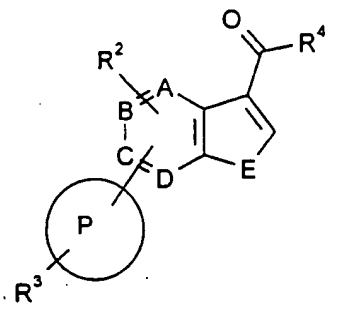
Pharmacological data

[^{3}H]-mesulergine binding to rat or human 5-HT_{2C} clones expressed in 293 cells in vitro

Compounds were tested following the procedure outlined in WO 94/04533. The compounds of examples 1 to 4 have pKi values of 7.5 to 8.1.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

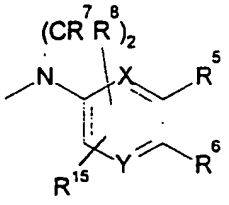
A,B,C and D are all carbon, or one of A,B,C or D is nitrogen and the others are carbon;

E is oxygen, sulphur, CH_2 or NR^1 where R^1 is hydrogen or C_{1-6} alkyl;

P is a phenyl or an optionally substituted 5-7-membered heterocyclic ring containing one to three heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 and R^3 are independently hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkylthio, CF_3, NR^9R^{10} or OR^{11} where R^9, R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or arylC_{1-6} alkyl; and

R^4 is a group of formula (i)



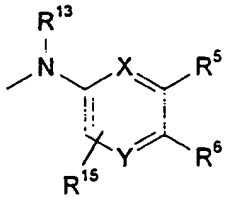
(i)

in which:

X and Y are both nitrogen, one is nitrogen and the other is carbon or a CR^{14} group or one is a CR^{14} group and the other is carbon or a CR^{14} group;

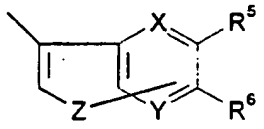
R^5, R^6, R^{14} and R^{15} groups are independently hydrogen, C_{1-6} alkyl optionally substituted by one or more halogen atoms, C_{2-6} alkenyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkylC_{1-6}alkoxy, C_{2-6} alkynyl, C_{3-6} cycloalkyloxy, C_{3-6} cycloalkyl-C_{1-6} alkyl, C_{1-6} alkylthio, C_{3-6} cycloalkylthio, C_{3-6} cycloalkyl-C_{1-6} alkylthio, C_{1-6}alkoxy, hydroxy, halogen, nitro, CF_3, C_2F_5, OCF_3, SCF_3, SO_2CF_3, SO_2F, formyl, C_{2-6} alkanoyl, cyano, optionally substituted phenyl or thienyl, NR^9R^{10}or

$CONR^9R^{10}$ where R^9 and R^{10} are as defined for R^1, CO_2R^{12} where R^{12} is hydrogen or C_{1-6} alkyl;
or R^5 and R^6 form part of an optionally substituted 5-membered carbocyclic or heterocyclic ring;
R^7 and R^8 are independently hydrogen or C_{1-6} alkyl; or
R^4 is a group of formula (ii):



(ii)

in which X and Y are both nitrogen, one is nitrogen and the other is a CR^{14} group or X and Y are both CR^{14} groups and R^5, R^6, R^{14} and R^{15} are as defined in formula (i); and
R^{13} is hydrogen or C_{1-6} alkyl, or
R^4 is a group of formula (iii):



in which R^5, R^6, X and Y are as defined for formula (i) and Z is oxygen, sulphur, CH_2 or NR^{13} where R^{13} is hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 in which P is pyridyl.
3. A compound according to claim 1 or 2 in which R^1 is hydrogen.
4. A compound according to any one of claims 1 to 3 in which R^2 is hydrogen.
5. A compound according to any one of claims 1 to 4 in which R^4 is a group of formula (i).
6. A compound according to any one of claims 1 to 5 in which R^5 and R^6 are C_{1-6}alkyl and C_{1-6}alkylthio.
7. A compound according to claim 1 which is:

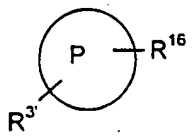
1-(5-(3-Pyridyl)-3-indolylcarbonyl-5-methoxy-6-trifluoromethylindoline,
1-(5-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
1-(6-(3-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
1-(6-(4-Pyridyl)-3-indolylcarbonyl)-5-methoxy-6-trifluoromethyl indoline,
and pharmaceutically acceptable salts thereof.

8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

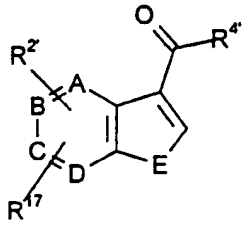
10. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



(II)

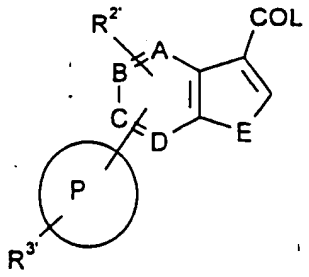
with a compound of formula (III);



(III)

wherein R^{16} and R^{17} contain the appropriate functional group(s) necessary to form a bond when coupled, A, B, C, D and P are as defined in formula (I), E is as defined in formula (I) or is a group $NR^{1'}$ and the variables, $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ are R^1, R^2, R^3 and R^4 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3 and R^4, interconverting R^1, R^2, R^3 and R^4 and forming a pharmaceutically acceptable salt thereof, or (b)

coupling a compound of formula (IV):



(IV)

wherein P, A, B, C, D, E, $R^{2'}$ and $R^{3'}$ are as defined above and L is a leaving group with a compound of formula (V):

$$R^{4'}\text{-}H \qquad (V)$$

wherein $R^{4'}$ is as defined above and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3 and R^4, interconverting R^1, R^2, R^3 and R^4 and forming a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Inte. ɔnal Application No
PCT/EP 96/03512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/14 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 14801 (SMITHKLINE BEECHAM PLC) 7 July 1994 see claims	1,9
A	WO,A,94 04533 (SMITHKLINE BEECHAM PLC) 3 March 1994 cited in the application see claims	1,9
A	WO,A,95 01976 (SMITHKLINE BEECHAM PLC) 19 January 1995 see claims	1,9
P,A	WO,A,96 23783 (SMITHKLINE BEECHAM PLC) 8 August 1996 see claims	1,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1996	19.11.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte. ...nal Application No
PCT/EP 96/03512

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9414801	07-07-94	NONE		
WO-A-9404533	03-03-94	AU-A-	4704693	15-03-94
		CA-A-	2142721	03-03-94
		CN-A-	1086819	18-05-94
		EP-A-	0656003	07-06-95
		JP-T-	8500580	23-01-96
		NZ-A-	254785	26-09-95
		SI-A-	9300438	31-03-94
		ZA-A-	9306050	20-02-95
WO-A-9501976	19-01-95	AP-A-	463	19-02-96
		AU-A-	7228394	06-02-95
		CA-A-	2166624	19-01-95
		EP-A-	0707581	24-04-96
WO-A-9623783	08-08-96	NONE		